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New cancer-fighting strategy focuses on signaling molecules

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Cancer researchers studying the immune system have identified a previously unrecognized set of targets and biomarkers to battle solid tumors.

The findings center on discovery of signaling molecules that are major players in a biochemical mechanism linking certain actions of B cells to solid tumor growth. The most notable implication of the study is that a drug in use for more than decade to treat non-Hodgkin's lymphoma, which is a cancer of the B cells, might be effective against other solid tumors, says lead author Lisa Coussens, PhD, of the UCSF Helen Diller Family Comprehensive Cancer Center.

"This is paradigm shifting," emphasizes Coussens, who is a pioneer in studying the role of molecular regulation in cellular inflammation that is linked to development of cancer. "The discoveries open up our thinking to many new signaling molecules as potential therapeutic targets."

The research is published online and in print by the scientific journal *Cancer Cell* (vol.17, issue 2, http://www.cell.com/cancer-cell/current).

"These are very significant findings because they suggest that Rituxan, a drug that we already are familiar with, could have very broad clinical implications in the treatment of some solid tumors," says Coussens, who also is a professor in the UCSF Department of Pathology and co-director of the Mouse Pathology Core and Program in Cancer, Immunity and Microenvironment.

The researchers found that a class of antibodies known as immunoglobulin G and the receptors to which they bind play a key role in the link between B cells and solid tumor growth. Called FcRgamma, these receptors are found on cells of the innate immune system (including mast cells, macrophages, and dendritic cells). The activation of FcRgamma plays a part in recruiting circulating immune cells to neoplastic (abnormal) tissue, which in turn enhances development of new blood vessels to feed nutrients to growing tumors and to advance progression to malignant cancer.

Most tumors are rife with activated immune cells, says Coussens, but their role in the development of cancer has been largely overlooked.

The findings may lead to more successful treatment of certain solid tumors by combining chemotherapy with drugs that can thwart cancer-promoting activities of the immune system, according to Coussens. For instance, the drug Rituxan has relatively few side effects, she adds.

As a result of the molecular discovery, Coussens is collaborating with pharmaceutical industry experts to explore new therapeutic strategies. Preclinical testing of the combination approach is underway involving therapies similar to Rituxan and chemotherapy, and initial results "look promising," says Coussens.

At UCSF, the Coussens lab focuses on the role of inflammatory cells and leukocyte proteases as critical regulators of skin, lung and breast cancer development. During the early development of cancer, many physiological processes occur in the vicinity of young tumor cells that are similar to processes that occur during embryonic development and to healing of wounds in adult tissue.

By studying mouse models of skin, lung and breast cancer development, the Coussens lab is identifying important molecules involved in

regulating tumor-associated inflammation, angiogenesis, and cancer development. Identification of these important regulatory mechanisms reveals drug-targets that can then be used to design novel therapeutic strategies for treating cancer development in humans.

Biochemical and cellular studies during the past decade have shown that inflammation can promote the development of cancer. In addition, certain chronic inflammatory conditions, such as Crohn's disease, pancreatitis, prostatitis, asbestosis and Barrett's esophagus, are associated with an elevated cancer risk.

Discoveries over the last decade have made clear that "Chronic inflammation in the context of tumor development is associated with a poor prognosis," says Coussens.

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